ADVERSE DRUG REACTIONS

The study of adverse drug reactions is known as ***pharmacovigilance***

Drugs are usually administered with the best of intentions, which is to have a beneficial therapeutic effect. However, all drugs have the potential to cause unwanted effects. These can range from being a minor or trivial to being life threatening.

These unwanted effects are known as ***adverse drug reactions***

This is a reaction to a drug that is always unwanted and may be harmful to the patients. It is a negative event following the prescription and administration of a medication.

The WHO defined ADR as " a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of "A physiological function".

ADRs present a major clinical problem.

According to the Department of Health (DoH,UK) approximately 4% of hospital admissions are associated with ADR (DoH,2001). In hospital, up to 20% of patients experience an adverse reaction.

The likelihood of drug interactions and adverse reactions is increased in patients on more than one medication and higher in those who take more than four medications (polypharmacy).

The incidence is also increased in elderly population as they may be on many drugs at the same time.

MANY CATEGORIES OF ADRs

Type A: Augmented effects

Type B: Bizarre effects

Type C : Chronic effects

Type D : Delayed effects

Type E : End-of-treatment effects

Type F : Failure of therapy.

TYPE A : AUGMENTED ADRs

The reaction here is an augmentation of the drug's pharmacology. this means we can often predict these reactions from our knowledge and experiences of the pharmacodynamic properties of a drug.

These types of reactions are mainly dose- related or dependent. The greater the dose of the drug, the higher the likelihood of adverse reactions.

Type A adverse drug reactions are mostly likely to occur with drugs that have a steep dose-response curve and small TR.

They are the most common ADRs, but are associated with lower morbidity and mortality.

Some examples of Type A adverse drug reactions

1) Patients on Diuretics

- Hypovolaemia
- Dehydration
- Hypokalaemia

2) Patients on Antihypertensive Drugs

Dizziness and Fainting due to too great or quick lowering of blood pressure.

3) Patients on Anticoagulant Drugs

4) NSAIDs--- can develop gastric irritation due tob the drug's Action on the protective gastric mucosa.

TYPE B : BIZARRE EFFECTS

The reaction here is wholly unexpected and could not be predicted from the pharmacodynamic properties of the drug. These kind of reactions are not dose –related and can occur even with low starting doses. They are rarer than ADRs and they are potentially more serious. Many are due to drug allergy and are associated with a high mortality and morbidity rate.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions to drugs involve immunological reactions. Large molecules such as vaccines, insulin and dextrans can provoke immune reactions themselves but most drugs are too small to be antigenic on their own.

In some patients, something that cannot be predicted is that a drug or drug metabolite can combine with tissue proteins to form an antigenic conjugate.

In this situation, the patient shows a response, which can be Described under one of the classical definitions of allergic reactions (that is Type 1 - Type 4) — initial exposure to the drug causing sensitization).

Subsequent exposure to the same drug triggers an immunological Reaction.

1) Type 1 anaphylaxis

- Most common allergic reaction. The allergen (drug) causes Production of IgE antibodies on first exposure. These antibodies attach themselves to mast cells. On subsequent exposure to the Same allergen, the combined IgE and allergen causes the mast cells to release a variety of chemicals including histamine.

2) TYPE 2 CYTOTOXIC REACTION

Some drugs bind to blood cell membranes. This makes the blood cells antigenic and results in the production of IgG antibodies against them. The antibodies so produced activate the complement system which destroys the blood cells.

RBCs-------HAEMOLYTIC ANAEMIA
WBCs------ agranulocytosis.
PLATELETS---thrombocytopenia

E.G. CARBIMAZOLE.

3) TYPE 3 immune complex reaction

Other drugs such as penicillin can form immune complexes with Antibodies IgG or IgM which circulate in the blood and can be Deposited in the joints, skin and kidneys causing local inflammation.

4) TYPE 4 CELL-MEDIATED REACTION

Here when drugs combine with proteins to form antigens, the T ymphocytes are activated and these cause damage to the skin Cells resulting in rashes, lumps and itchy weeping skin. This type Of allergic reaction is possible in response to local anaesthetics.

MAJOR GROUPS OF DRUGS INVOLVED IN ADRs

Some drugs are more likely to cause ADRs than others. This indicates that their prescribing and administration should be closely monitored.

These groups of drugs include :

- Antibiotics
- Antipsychotics
- Nsaid
- Drugs with a narrow therapeutic index e.g. Warfarin and Digoxin.
- Lithium
- Diuretics
- Benzodiazepines

STEPS IN MINIMIZING THE EFFECTS OF ADRs

There are a variety of steps that can be taken to minimise or prevent ADRs:

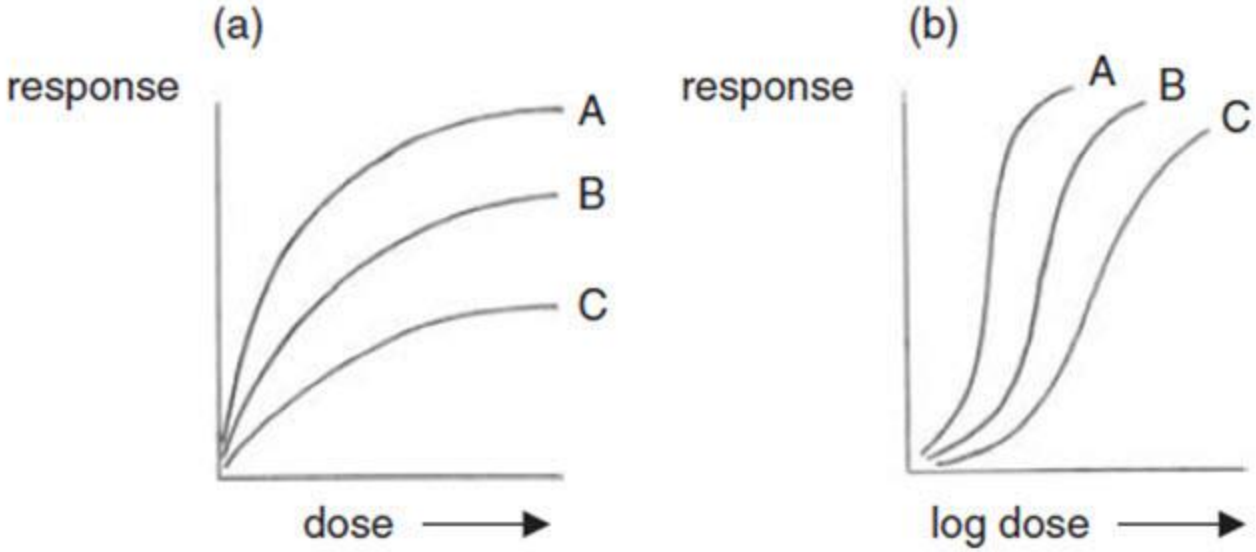
1) Drugs should only be prescribed for a good indication(should be justified).
2) A check should be made on all previous medication (past drug history).
3) Check for previous reactions to medications (History of previous reactions to drugs)
4) Other drug use should be verified (OTC).
5) Assess or check for any hepatic and renal problems.
6) Prescribing of medications should be according to hospital drug policies.

7) Administration of drugs should always be according to policies.

8) Clear instructions and details of the drugs should always be provided to the patients---leaflets, medication awareness group, website.

9) Always inform the patient of the possible side effects to help them identify ADRs.

10) Nurse Practitioners ‘ roles and responsibilities in relation to drugs.



(a) relationship between drug dose (concentration) plotted against response to the drug for three drugs, drug A, drug B and drug C

(b) relationship between log dose plotted against response to drug
log dose curves are plotted because they are easier to interpret: at the steepest point, small changes in drug concentration result in large changes in response; drug A is more likely to produce an adverse reaction than drug B or C

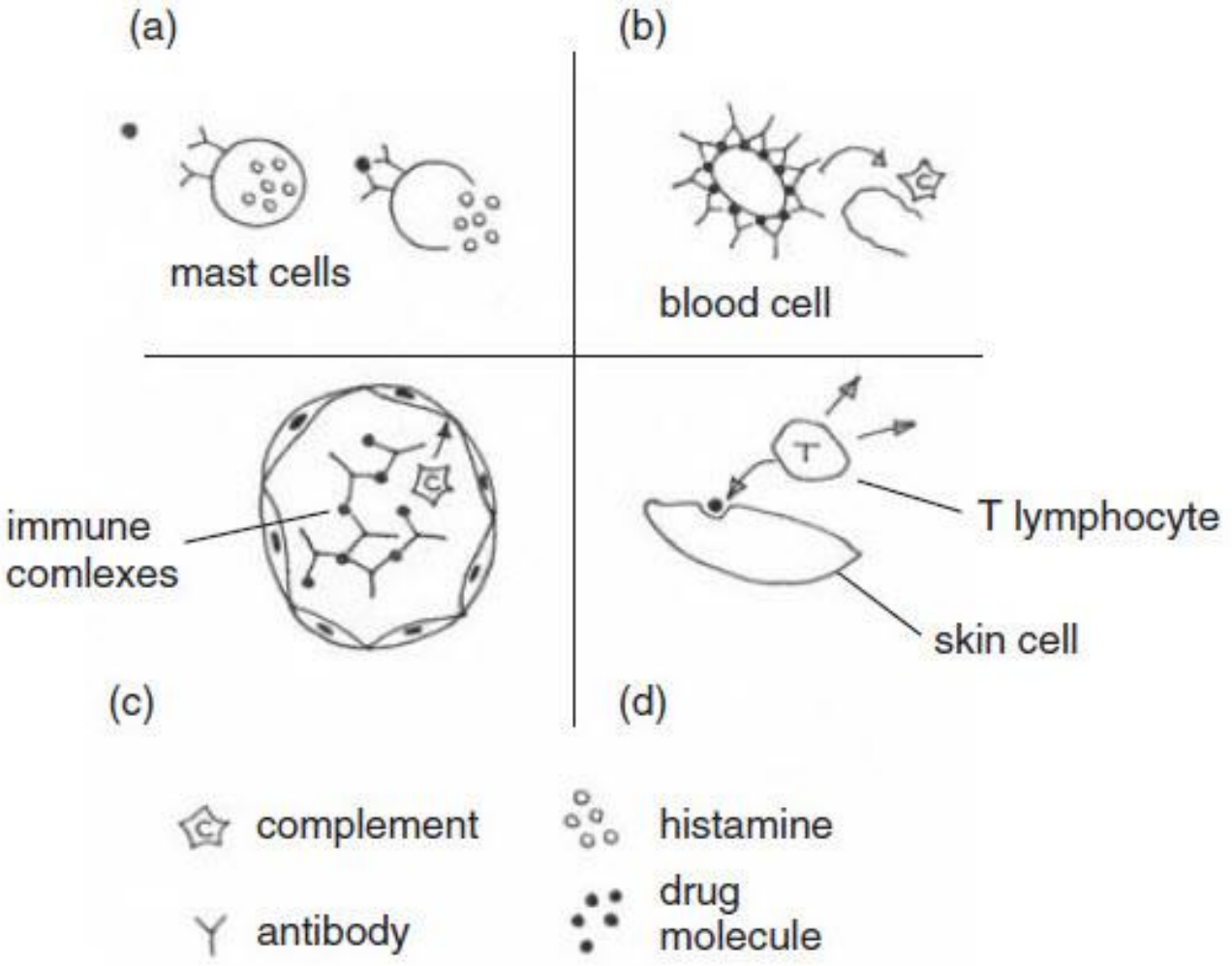
Dose–response curve

Mechanisms of drug–drug interactions

Mechanism	Effect	Example
Potentiation	Actions of drugs with similar actions are additive	Central nervous system depression with benzodiazepines and alcohol
Opposite effects	Drugs with opposite effects cancel out each other's activity.	β receptor stimulants (bronchodilators) and β receptor blockers (antihypertensives)
Altered absorption	Absorption can be increased or decreased by the actions of another drug	Opiates slow intestinal transit time and increase absorption of other drugs Tetracycline can reduce absorption of iron salts
Competition for protein binding	Drugs compete for the same plasma protein binding sites	Warfarin and aspirin displace each other from binding sites
Enzyme induction	Drug induces increased activity of enzymes [a]	Alcohol induces enzymes that metabolize warfarin
Enzyme inhibition	Drug inhibits activity of enzymes[a]	Cimetidine (for stomach ulcers) inhibits enzymes that metabolize warfarin
Altered excretion	Competition for transport systems in kidney	Elimination of methotrexate (cancer chemotherapy) inhibited by probenecid (for gout)

Type A adverse drug reactions

Cause	Effect
Overdose	Incorrect dosage/correct dose, wrong route; causes increased plasma levels
Age – old and very young	Metabolism and excretion less efficient Distribution varies with different body composition
Disease	Pharmacokinetics altered in disease states, especially of liver and kidney
Genetic variation	Different enzyme activity
Drug-drug interaction	Increased/reduced effect of one or more drugs



(a) Type 1 anaphylaxis
(b) Type 2 cytotoxic reaction
(c) Type 3 immune complex reaction
(d) Type 4 cell-mediated reaction

Hypersensitivity reactions